

4.7 INFLUENZA

4.7.1 Virology

The influenza viruses are single-stranded RNA orthomyxoviruses. They are classified antigenically as types A, B or C, but generally only influenza A and B cause severe disease in humans.¹ Influenza viruses possess two surface glycoprotein antigens: the haemagglutinin (H), which is involved in cell attachment during infection, and the neuraminidase (N), which facilitates the release of newly synthesised virus from the cell. Influenza A viruses can be classified into subtypes based on differences in these surface antigens, whereas influenza B cannot. Antibody against the surface antigens, particularly the haemagglutinin, reduces infection or severe illness due to influenza.

Both influenza A and influenza B viruses undergo frequent changes in their surface antigens, involving stepwise mutations of genes coding for H and N glycoproteins. This results in cumulative changes in influenza antigens, or 'antigenic drift', which is responsible for the annual outbreaks and epidemics of influenza and is the reason that the composition of influenza vaccines requires annual review. 'Antigenic shift', defined as a dramatic change in influenza A H (and other) antigen(s), occurs occasionally and unpredictably and can cause pandemic influenza.¹ Pandemic subtypes arise following antigenic shift, which is due to direct adaptation to humans of an avian or animal virus, or to this adaptation occurring by genetic reassortment (mixing) with a human virus.

4.7.2 Clinical features

Influenza is transmitted from person to person by virus-containing respiratory aerosols produced during coughing or sneezing, or by direct contact with respiratory secretions.^{1,2} Influenza virus infection causes a wide spectrum of disease, from no or minimal symptoms, to respiratory illness with systemic features, to multisystem complications and death from primary viral or secondary bacterial pneumonia. Severe disease from seasonal influenza is more likely with advanced age; infancy; lack of previous exposure to antigenically related influenza virus; greater virulence of the viral strain; chronic conditions, such as heart or lung disease, renal failure, diabetes and chronic neurological conditions; immunocompromise; obesity (class III); pregnancy; and smoking. Severe disease may also occur in otherwise healthy children and young adults. Annual attack rates in the general community are typically 5 to 10%, but may be up to 20% in some years. In households and 'closed' populations, attack rates may be 2 to 3 times higher.^{3,4} However, as asymptomatic or mild influenza illness is common and symptoms are non-specific, a large proportion of influenza infections are not detected.

In adults, the onset of illness due to influenza is often abrupt, usually after an incubation period of 1 to 3 days, and includes systemic features such as malaise, fever, chills, headache, anorexia and myalgia. These may be accompanied by a cough, nasal discharge and sneezing. Fever is a prominent sign of infection and peaks at the height of the systemic illness. Symptoms are similar for influenza A and B viruses. However, infections due to influenza A (H3N2) strains are more likely to lead to severe morbidity and increased mortality than influenza B or seasonal influenza A (H1N1) strains.^{1,2}

The clinical features of influenza in infants and children are similar to those in adults. However, temperatures may be higher in children (and may result in febrile convulsions in this susceptible age group), and otitis media and gastrointestinal manifestations are more prominent.⁵ Infection in young infants may be associated with more non-specific symptoms.^{5,6}

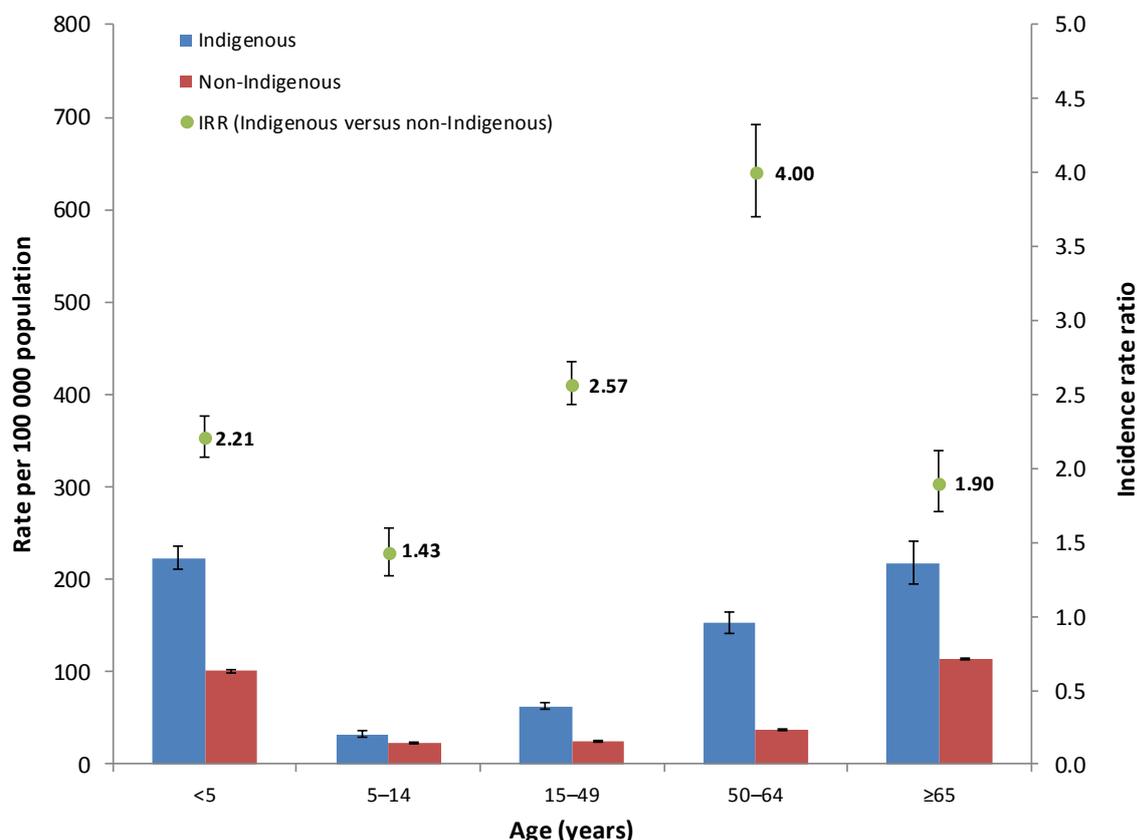
Complications of influenza include: acute bronchitis, croup, acute otitis media, pneumonia (both primary viral and secondary bacterial pneumonia), cardiovascular complications including myocarditis and pericarditis, post-infectious encephalitis, Reye syndrome, and various haematological abnormalities. Primary viral pneumonia occurs rarely, but secondary bacterial pneumonia is a frequent complication in persons whose medical condition makes them vulnerable to the disease. Such persons are at high risk in epidemics and may die of pneumonia or cardiac decompensation.

4.7.3 Epidemiology

In most years, minor or major epidemics of type A or type B influenza occur, usually during the winter months in temperate regions. It has long been recognised that the impact of influenza is often substantially under-estimated. On average each year in Australia, approximately 100 deaths and 5100 hospitalisations are recorded as being directly attributable to influenza.^{7,8} In the 2017 influenza season, the highest levels of activity since the 2009 pandemic year were recorded. Systematic introduction of rapid influenza testing in hospitals in New South Wales may have contributed in part to the increased number of laboratory-confirmed notifications of influenza. Approximately 750 deaths were reported nationally among notified cases of laboratory-confirmed influenza in 2017.⁹ A study using mathematical modelling estimated that there are over 3000 deaths and more than 13 500 hospitalisations due to influenza per year among Australians aged over 50 years.¹⁰ Another mathematical modelling study estimated the annual rate of seasonal influenza A mortality to be as high as 25.8 per 100 000 population in Australians aged ≥ 65 years.¹¹ Influenza activity varies from year to year and is dependent on the circulating virus and the susceptibility of the population.^{10,12} Changes in influenza detection methods, such as an increase in the routine use of polymerase chain reaction (PCR)-based laboratory testing in recent years, has impacted influenza detection and notification patterns.¹³

In Australia, like other developed countries, the highest rates of influenza hospitalisations are seen in the elderly and in children <5 years of age (Figure 4.7.1).^{8,12,14,15} The disease burden from influenza is greater in Aboriginal and Torres Strait Islander people than in non-Indigenous Australians, across all age groups.¹⁶ During annual epidemics of influenza, a greater rise in morbidity and mortality is seen among pregnant women and people with chronic diseases compared with otherwise healthy individuals.¹⁷⁻¹⁹

Figure 4.7.1: Average annual influenza hospitalisation rates for 2010 to 2015,* Australia, by age group and Indigenous status



* Hospitalisations (ICD-coded; principal diagnosis) where the month of admission was between January 2010 and December 2015.
IRR = incidence rate ratio

Three influenza pandemics were recognised in the 20th century, in 1918 (H1N1), 1957 (H2N2) and 1968 (H3N2). Each of these pandemic strains replaced the previously circulating influenza A subtype and went on to circulate as seasonal influenza. In 1977, the A (H1N1) re-emerged in the human population and, since then, A (H1N1) and A (H3N2) have co-circulated with influenza B. More recently, various avian influenza A virus subtypes, particularly H5N1, H7N9 and H9N2, have caused human infections, but sustained human-to-human transmission has not been reported.^{20,21}

In 2009, the World Health Organization (WHO) declared a pandemic of a novel subtype A (H1N1) influenza virus, A(H1N1)pdm09, which originated in swine. The pandemic started in Mexico and the United States before spreading globally.²² There were 44 403 confirmed A(H1N1)pdm09 cases and 213 deaths in Australia between May 2009 and November 2010.²³ The predominant clinical presentation was mild to moderate illness; however, risk factors for severe disease included obesity, pregnancy, diabetes mellitus and, in Australia, being of Aboriginal or Torres Strait Islander descent (refer to 3.1 *Vaccination for Aboriginal and Torres Strait Islander people*). Young healthy adults and pregnant women were over-represented among severe A(H1N1)pdm09 cases compared with previous seasonal outbreaks. The A(H1N1)pdm09 virus rapidly established itself and has become the dominant influenza strain in most parts of the world.^{2,24} This strain has been included in all seasonal influenza vaccine formulations used in the southern hemisphere since 2010.

Since the early 2000s, two influenza B lineages, B/Victoria and B/Yamagata, have been co-circulating in Australia in varying proportions; in some years one B lineage predominates over the other, while in other years both B lineages co-circulate in similar proportions.^{25,26}

4.7.4 Vaccines

All the influenza vaccines currently available in Australia are either split virion or subunit vaccines prepared from purified inactivated influenza virus that has been cultivated in embryonated hens' eggs. Although these vaccines may contain traces of egg-derived protein (ovalbumin) they contain less than 1 µg of ovalbumin per dose (refer also to 4.7.10 *Precautions* below and to 'Vaccination of persons with a known egg allergy' in 3.3.1 *Vaccination of persons who have had an adverse event following immunisation*).

The influenza virus composition of vaccines for use in Australia is determined annually by the Australian Influenza Vaccine Committee following recommendations by the World Health Organization based on global influenza epidemiology.²⁷

From the late 1970s, influenza vaccines contained three strains of influenza virus – two influenza A subtypes and one influenza B lineage (i.e. trivalent influenza vaccines or TIVs). Inactivated quadrivalent influenza vaccines (QIVs) containing four influenza virus strains (the same strains in TIV and an additional influenza B virus strain from the other B lineage) have been registered for use in Australia since 2014 and in widespread use since 2016. Quadrivalent vaccines currently registered for use in persons aged ≥3 years contain 15 µg of haemagglutinin (HA) from each of the four virus strains and they are not adjuvanted. The 'junior' quadrivalent influenza vaccine registered for use from 6 months to <3 years of age contains 7.5 µg of HA from each virus strain. From 2018, two trivalent vaccines are registered for use in adults aged ≥65 years: one is a 'high-dose' vaccine that contains four times the HA content of standard trivalent vaccines (i.e. 60 µg HA per included virus strain per dose); the other contains an adjuvant, MF59, and the standard 15 µg of HA per strain per dose. Both vaccines are formulated to induce a greater immune response than standard TIVs.

A live attenuated intranasal influenza vaccine is registered in Australia but is not currently available.²⁸ Influenza vaccines presented in a purpose-designed syringe for intradermal administration were registered for use in Australia in 2009 but are no longer available.

Always check annual seasonal influenza vaccine availability statements on www.immunise.health.gov.au. Vaccines and age eligibility change from year to year.

Children aged ≥6 months to <3 years only

- **FluQuadri Junior** – Sanofi-Aventis Australia Pty Ltd (quadrivalent inactivated influenza virus). Each 0.25 mL pre-filled syringe contains 7.5 µg haemagglutinin of each of the four recommended influenza virus strains; ≤50 µg formaldehyde; ≤125 µg octoxinol 9; ≤0.5 µg ovalbumin.

All persons aged ≥3 years

- **Fluarix Tetra** – GlaxoSmithKline Australia Pty Ltd (quadrivalent inactivated influenza virus). Each 0.5 mL pre-filled syringe contains 15 µg haemagglutinin of each of the four recommended influenza virus strains; ≤0.05 µg ovalbumin; ≤5 µg formaldehyde; polysorbate 80; octoxinol 10. May contain traces of gentamicin, hydrocortisone and sodium deoxycholate.
- **FluQuadri** – Sanofi-Aventis Australia Pty Ltd (quadrivalent inactivated influenza virus). Each 0.5 mL pre-filled syringe contains 15 µg haemagglutinin of each of the four recommended influenza virus strains; ≤100 µg formaldehyde; ≤250 µg octoxinol 9; ≤1 µg ovalbumin.

All adults aged ≥18 years

- **Afluria Quad** – Seqirus (quadrivalent inactivated influenza virus). Each 0.5 mL pre-filled syringe contains 15 µg haemagglutinin of each of the four recommended influenza virus strains; <1 µg ovalbumin. May contain traces of sodium taurodeoxycholate, neomycin, polymyxin B and β-propiolactone.
- **Influvac Tetra** – Mylan Health Pty Ltd (quadrivalent inactivated influenza virus). Each 0.5 mL pre-filled syringe contains 15 µg haemagglutinin of each of the four recommended influenza virus strains; ≤100 ng ovalbumin; ≤0.01 mg formaldehyde; 0.02 mg cetrimeronium bromide; 1 ng gentamicin sulfate. May contain traces of tylosine tartrate, hydrocortisone and polysorbate 80.

Adults aged ≥65 years only

- **Fluad** – Seqirus (adjuvanted trivalent inactivated influenza virus). Each 0.5 mL pre-filled syringe contains 15 µg haemagglutinin of each of the three recommended influenza virus strains, adjuvanted with MF59C.1 (which includes 9.75 mg squalene and 1.175 mg polysorbate 80). May contain traces of kanamycin, neomycin, formaldehyde, barium sulphate, cetyltrimethylammonium bromide and ovalbumin.
- **Fluzone High-Dose** – Sanofi-Aventis Australia Pty Ltd (trivalent inactivated influenza virus). Each 0.5 mL pre-filled syringe contains 60 µg haemagglutinin of each of the three recommended influenza virus strains; <1 µg ovalbumin; ≤100 µg formaldehyde; ≤250 µg octoxinol 9.

The administration of influenza vaccine is the single most important measure in preventing or attenuating influenza infection and preventing mortality. After vaccination, most recipients develop antibody levels that are likely to protect them against the strains of virus represented in the vaccine. In addition, there is likely to be protection against many related influenza variants.

The efficacy and effectiveness of influenza vaccines of similar composition depends primarily on the age and immunocompetence of the vaccine recipient, and the degree of similarity between the virus strains in the vaccine and those circulating in the community.²⁹⁻³⁷ The magnitude of the potential additional benefit from QIV over TIV (due to protection against the additional B strain) cannot be predicted for any influenza season as it depends on a number of factors. These include annual variation in the proportion of all circulating influenza viruses that is attributable to the influenza B lineage not in the TIV,²⁵ antigenic mismatch between vaccine and circulating strains, cross-protection against non-vaccine B strains afforded by the strain in the TIV, and an individual's pre-existing immunity to the circulating strains of influenza. Recent evidence estimated QIV to be 54% effective against laboratory-confirmed influenza.³⁸

In a clinical trial, the trivalent vaccine with greater HA content (Fluzone High-Dose) was estimated to be 24% more effective against laboratory-confirmed influenza compared to standard TIV,³⁹ and to be 2 to 36% more effective than standard TIV in reducing influenza-related deaths.⁴⁰ In a large post-licensure study of community-dwelling adults aged ≥ 65 years, the adjuvanted TIV (Fluad) was estimated to be 25% more effective against hospitalisation for influenza or pneumonia compared to standard TIV.⁴¹ However, compared with QIVs, the potential for improved protection from these two more immunogenic TIVs is counter-balanced by the potential loss of protection against the second B lineage (conferred by QIVs), and also by increased injection site reactions^{42,43} (refer to 4.7.11 *Adverse events* below). In persons aged ≥ 65 years, however, disease from the A/H3 influenza strain is more common and associated with greater severity. Therefore, in this age group, the potential additional protection provided by these two TIVs against the strains included in the vaccine is likely to offset the loss of protection against the alternative B strain not included in the vaccine. In a clinical trial among adults aged ≥ 65 years, the TIV with greater HA content (Fluzone High-Dose) was estimated to be 23% more effective against laboratory-confirmed A/H3 influenza compared to the standard TIV.⁴⁰

A recent systematic review estimated the overall efficacy of standard TIV against laboratory-confirmed influenza in healthy adults < 65 years of age to be 59%, although efficacy varied by influenza season.⁴⁴ The efficacy of inactivated standard TIV against influenza-like illness in persons ≥ 65 years of age living in the community is estimated to be 43% when viral circulation is high, although there have been few randomised controlled trials of influenza vaccine in elderly people.⁴⁵ In nursing home settings, TIV is approximately 45% effective against hospitalisations due to influenza and pneumonia, and 60% effective against all-cause mortality in persons aged ≥ 65 years.⁴⁵

Vaccination of pregnant women with standard TIV has been shown to be approximately 50% effective in reducing PCR-confirmed influenza infection and 65% effective against inpatient hospital admissions for acute respiratory illness.^{46,47} Vaccinating pregnant women against influenza also provides protection against laboratory-confirmed influenza to their infants up to 6 months of age, due to transplacental transfer of high titre influenza-specific antibodies. A recent systematic review concluded that maternal influenza vaccination results in an estimated 48% reduction in laboratory-confirmed influenza in infants < 6 months of age.⁴⁸

Young children can be vaccinated from 6 months of age, but, because they are immunologically naive to influenza, they require 2 doses of influenza vaccine when immunised for the first time, to maximise the immune response to all vaccine strains.^{55,56} There is evidence demonstrating that similar levels of protection are achieved in young children as in older children and adults, with an estimated vaccine effectiveness of 65% against laboratory-confirmed influenza in those aged 6 to 59 months.⁴⁹⁻⁵⁴

Recent evidence suggests that protection following influenza vaccination may begin to wane after 3 to 4 months.^{52,55-60} Low levels of protection may persist for a further year for some strains, if the prevalent circulating strain remains the same or undergoes only minor antigenic drift.^{29,37}

Protection against influenza requires annual vaccination with a vaccine containing the most recent strains. Studies of the impact of repeated annual vaccination on year-to-year vaccine effectiveness have produced conflicting results. A few studies, predominantly in the United States, suggest a reduction in vaccine effectiveness after repeated annual influenza vaccination.^{61,62} However, an Australian study has reported sustained or increased vaccine effectiveness in preventing both influenza A and B illness and hospitalisation, particularly among children aged 2–8 years who have received influenza vaccination in previous seasons.⁶³ Benefit from annual influenza revaccination is also observed among community-dwelling elderly people. Data collected over six influenza seasons shows annual influenza revaccination among community-dwelling elderly people is associated with a 15% reduction in the risk of annual mortality compared to first-time vaccination.⁶⁴ Overall, despite conflicting opinion regarding the impact of repeated annual vaccination on vaccine effectiveness, greater protection against influenza infection is still observed among individuals who received influenza vaccination compared to those who did not receive any influenza vaccination.

4.7.5 Transport, storage and handling

Transport according to *National vaccine storage guidelines: Strive for 5*.⁶⁵ Store at $+2^{\circ}\text{C}$ to $+8^{\circ}\text{C}$. Do not freeze. Protect from light.

Influenza vaccines should be appropriately discarded when they reach their expiry date to avoid inadvertently using a product with the incorrect formulation in the following year.

4.7.6 Dosage and administration

Vaccines registered by the TGA, and the ages for which they are indicated, can change from year to year. Always check annual seasonal influenza vaccine availability statements published by ATAGI on the Immunise Australia website (www.immunise.health.gov.au), and consult individual product information.

Refer to Table 4.7.1 for the recommended doses of influenza vaccine for different age groups. For adults aged ≥ 65 years who have already received either a high-dose or adjuvanted TIV in the current influenza season, a further dose of QIV in the same season is not recommended, although not contraindicated.

Influenza vaccines available in Australia are presented in pre-filled syringes, of either 0.5 mL or 0.25 mL. Some 0.5 mL syringes have a graduated mark to indicate where the plunger can be depressed to provide a 0.25 mL dose if indicated.

Children aged 6 months to <3 years require a 0.25 mL dose. If a child aged 6 months to <3 years inadvertently receives a 0.5 mL dose of influenza vaccine, no immediate action is necessary. There is some evidence that a 0.5 mL dose of inactivated influenza vaccine is immunogenic in children <3 years of age, and evidence that a 0.5 mL dose is safe in this age group (apart from Afluria Quad).^{66,67} Any additional dose(s) required in that season or in future seasons should be given following standard recommendations (refer to Table 4.7.1).

Shake the pre-filled syringe vigorously before injection.

The preferred route of administration for influenza vaccines is by IM injection; however, they may also be given by the SC route (refer to Table 2.2.1 *Route of administration for vaccines used in Australia*).

Table 4.7.1: Recommended doses of influenza vaccine

Age	Dose	Number of doses required	
		In the first year of influenza vaccination	If previously received 1 or more doses of influenza vaccine
6 months to <3 years*	0.25 mL [†]	2	1
≥ 3 years to <9 years*	0.5 mL [‡]	2	1
≥ 9 years	0.5 mL [‡]	1 [§]	1

* Children aged 6 months to <9 years receiving influenza vaccine for the first time require 2 doses, at least 4 weeks apart, to maximise the immune response to the vaccine strains. For children who have previously received 1 or more doses of trivalent or quadrivalent influenza vaccine, only 1 dose of influenza vaccine is required in the current season and all seasons thereafter (irrespective of whether TIV or QIV is being used).^{68,69}

[†] If a child aged 6 months to <3 years inadvertently receives a 0.5 mL dose of influenza vaccine, no immediate action is necessary, and any additional dose(s) required that season or in future seasons should be given following standard recommendations.

[‡] If a child aged ≥ 3 years or an adult inadvertently receives a 0.25 mL dose of influenza vaccine, an additional 0.25 mL should be administered immediately. If the error is discovered later (after the patient has left the vaccination setting), a full age-appropriate dose (0.5 mL) should be administered as soon as the patient can return. Any additional dose(s) required that season or in future seasons should then be given following standard recommendations.

[§] Two doses, at least 4 weeks apart, are recommended for persons with certain immunocompromising conditions (i.e. haematopoietic stem cell transplant or solid organ transplant) receiving influenza vaccine for the first time post transplant (irrespective of their age) (refer to 4.7.7 *Recommendations below and 3.3 Groups with special vaccination requirements*).

Co-administration with other vaccines

All inactivated influenza vaccines can be administered concurrently with any other vaccine, including pneumococcal polysaccharide vaccine, zoster vaccine and all scheduled childhood vaccines. Parents/carers of infants or children who are recommended to receive both influenza vaccine and 13-valent pneumococcal conjugate vaccine (13vPCV) should be advised of a possible small increased risk of fever following concomitant administration of these vaccines (refer to 4.7.10 *Precautions below and 4.13 Pneumococcal disease*).

Interchangeability of influenza vaccines

Where 2 doses of influenza vaccine are indicated in a single season (refer to Table 4.7.1 *Recommended doses of influenza vaccine*), different brands are considered interchangeable (providing they are age-appropriate).

Timing of influenza vaccination

Influenza vaccination can be offered from the time the vaccine becomes available, typically in March or April, although the exact timing can vary from year to year. Annual influenza vaccination before the onset of each influenza season is recommended. The period of peak influenza circulation is typically between June and September for most parts of Australia, but influenza can still occur year round, particularly in tropical areas. Recent evidence suggests that while protection is generally expected to last for the whole season, optimal protection against influenza occurs within the first 3 to 4 months following vaccination. Although deferring vaccination to a time point closer to the winter months may result in greater immunity later in the season, it may also result in missed opportunities for vaccination and lack of protection in the event of an early onset influenza season. Providers need to weigh up the above factors for each individual and, in addition, balance this with the challenge of vaccinating large numbers of individuals within a constrained time period. Vaccination should be offered throughout the influenza season. In particular, pregnant women and travellers can benefit from vaccination at any time of the year. Children receiving their first lifetime dose should be vaccinated as soon as possible after the vaccine becomes available to ensure there is sufficient time to receive a second dose (recommended ≥ 4 weeks later) before the influenza season commences.

4.7.7 Recommendations

Annual influenza vaccination is recommended for all persons ≥ 6 months of age.^{5,6,70,71}

A single annual dose of influenza vaccine is recommended for most individuals; revaccination later in the same season is not recommended, although not contraindicated. Two doses at least 4 weeks apart are recommended for children aged 6 months to < 9 years receiving influenza vaccine for the *first* time and persons receiving influenza vaccine for the *first* time post haematopoietic stem cell or solid organ transplant (irrespective of their age).

Influenza vaccination is particularly strongly recommended for the following groups:

All children aged < 5 years

Infants and children aged < 5 years have a higher risk of hospitalisation and increased morbidity following influenza (Figure 4.7.1).¹² This includes young children without pre-existing medical conditions who are at greater risk of hospitalisation compared with older children and adults.^{17,72,73} Specific brands of influenza vaccine are registered by the TGA for use in children from 6 months of age and these may change from year to year (refer to 4.7.4 *Vaccines* and 4.7.6 *Dosage and administration* above).

All adults aged ≥ 65 years

Influenza-associated mortality rates are highest among adults aged ≥ 65 years.⁸ Evidence shows that influenza vaccine reduces hospitalisations from influenza and pneumonia and all-cause mortality in adults ≥ 65 years of age.⁴⁵ The high-dose (Fluzone High-Dose) and adjuvanted (Fluad) TIVs are preferentially recommended over QIVs for adults aged ≥ 65 years. However, there is no preference for use between these two TIVs. (Refer also to 4.7.4 *Vaccines* above.)

Aboriginal and Torres Strait Islander people

Annual influenza vaccination is recommended for all Aboriginal and Torres Strait Islander people. The disease burden from influenza is significantly higher among Aboriginal and Torres Strait Islander people than in non-Indigenous Australians, across all age groups (refer to 4.7.3 *Epidemiology* above and 3.1 *Vaccination for Aboriginal and Torres Strait Islander people*).⁸

Pregnant women

Influenza vaccination is recommended for pregnant women in every pregnancy due to the increased risk of morbidity and mortality from influenza during pregnancy.¹⁸ The risk to the mother of complications from influenza increases in the later stages of pregnancy as does the potential for pre-term delivery.⁷⁴⁻⁸³ Influenza vaccination of pregnant women also protects their infants from influenza in early infancy, due to transplacental transfer of high-titre antibodies from the vaccinated woman to the fetus.^{75,84,85} Influenza vaccine can be given during any stage of pregnancy; the timing of vaccination should be considered in relation to the influenza season and vaccine availability. Influenza vaccine should be given as early as practicable in each pregnancy. If not already given, influenza vaccine can be administered concurrently with the dTpa vaccine, recommended for administration early in the third trimester (refer to 4.12 *Pertussis*). Pregnant women who may have received the previous years' seasonal influenza vaccine early in their pregnancy can receive the current seasonal influenza vaccine (when it becomes available) later in the same pregnancy.

Clinical risk groups

Influenza vaccination is recommended for persons aged ≥ 6 months with conditions predisposing them to severe influenza,⁷ such as:

- *Cardiac disease*, including cyanotic congenital heart disease, coronary artery disease and congestive heart failure – Influenza causes increased morbidity and mortality in children with congenital heart disease and adults with coronary artery disease and congestive heart failure.^{71,86-89}

- *Down syndrome* – Persons with Down syndrome should receive annual seasonal influenza vaccine whether or not they have congenital heart disease. This is due to the presence of anatomical abnormalities, which put them at increased risk of upper respiratory tract infections, as well as a high prevalence of other medical conditions that put them at increased risk of severe influenza.⁸⁸
- *Obesity* – Persons with a BMI ≥ 40 kg/m² (classified as class III obesity) should receive annual seasonal influenza vaccine due to their increased risk of severe outcomes, particularly observed following infection with the A(H1N1)pdm09 influenza strain.⁹⁰⁻⁹³ This increased risk is independent of the presence of underlying comorbidities.⁹⁴ There is also some evidence that persons who have a BMI between 30 and <40 (class II obesity) are at increased risk of severe influenza and may benefit from annual influenza vaccine.^{92,94,95} Studies assessing the association of obesity and severe outcomes following infection with the A(H1N1)pdm09 strain demonstrate the greatest risk is in those with the highest BMI.^{90,92,93,96}
- *Chronic respiratory conditions*, including:
 - » suppurative lung disease, bronchiectasis and cystic fibrosis^{71,87} – Patients with these diseases are at greatly increased risk from influenza, which may cause irreversible deterioration in lung function.⁹⁷
 - » chronic obstructive pulmonary disease (COPD) and chronic emphysema^{71,98,99} – Data from several studies provide evidence that influenza vaccination has a clinically important protective effect on influenza-related COPD exacerbations, and probably an effect on the total number of exacerbations in COPD patients.^{98,99}
 - » severe asthma – In patients with severe asthma, defined as requiring frequent medical consultations or the use of multiple medications, annual influenza vaccine is an important part of routine care.^{71,87} Influenza can cause severe exacerbations of wheezing, and about 10% of episodes of virus-induced wheezing are attributable to influenza.
- *Chronic neurological conditions* (e.g. multiple sclerosis, spinal cord injuries, seizure disorders or other neuromuscular disorders) – These conditions can compromise respiratory function or the expulsion of respiratory secretions that can then increase the risk for aspiration.^{71,87} Influenza vaccination is particularly important for children ≥ 6 months of age with chronic neurological conditions as these children can experience severe, even fatal, influenza.
- *Immunocompromising conditions* – Persons who are immunocompromised, including those with HIV infection, malignancy, functional or anatomical asplenia (which includes sickle cell disease or other haemoglobinopathies, congenital or acquired asplenia, splenic dysfunction), or chronic steroid use, are at an increased risk from influenza (refer to 3.3.3 *Vaccination of immunocompromised persons*).^{71,87} They may also have a reduced immune response to influenza vaccine, although vaccination does afford some protection.¹⁰⁰ Influenza vaccination is recommended annually in all immunocompromised patients aged ≥ 6 months.

For patients with cancer who are receiving treatment with immuno-oncology therapies including CTLA-4 inhibitors (e.g. ipilimumab) and/or PD-1 and PD-L1 inhibitors (e.g., nivolumab, pembrolizumab), the treating oncologist should be consulted regarding the optimal timing of influenza vaccination.

Persons with certain immunocompromising conditions (i.e. haematopoietic stem cell transplant or solid organ transplant) receiving influenza vaccine for the first time post transplant are recommended to receive 2 vaccine doses at least 4 weeks apart (irrespective of age) and 1 dose annually thereafter (refer to 3.3.3 *Vaccination of immunocompromised persons*). Where it is known that a new influenza vaccine strain is circulating in the community to which cross-protective immunity in the population is low (such as in the setting of an influenza pandemic), it may be appropriate that immunocompromised persons receive 2 doses of inactivated influenza vaccine, a minimum of 4 weeks apart, to achieve an optimal immune response, irrespective of their previous influenza vaccination history. For example, in the 2009–2010 H1N1 global influenza pandemic it was shown that seroconversion to influenza vaccination in immunocompromised adolescents and adults was improved following receipt of 2 vaccine doses.¹⁰¹

While patients with advanced HIV disease and low CD4⁺ T-lymphocyte counts may not develop protective antibody titres after vaccination, there is evidence that individuals with minimal symptoms and high CD4⁺ T-lymphocyte counts develop protective antibody titres after influenza vaccination. Influenza vaccine has been shown to reduce the incidence of influenza in HIV-infected patients, and, although viral load may increase transiently, there was no impact on CD4⁺ count.¹⁰⁰ (Refer also to 3.3 *Groups with special vaccination requirements*, Table 3.3.4.)

- *Chronic liver disease* – Persons with histological evidence of fibrosis or cirrhosis and/or clinical evidence of chronic liver disease due to various causes, including alcoholism, are at increased risk of severe outcomes following influenza infection.^{18,92,102}
- *Other chronic illnesses* requiring regular medical follow-up or hospitalisation in the preceding year, including:
 - » diabetes mellitus^{71,87,103}

- » chronic renal failure^{71,87}
- » chronic inherited metabolic diseases (which includes amino acid disorders, carbohydrate disorders, cholesterol biosynthesis disorders, fatty acid oxidation defects, lactic acidosis, mitochondrial disorders, organic acid disorders, urea cycle disorders, vitamin/cofactor disorders, porphyrias)^{71,87}
- *Long-term aspirin therapy in children* (aged 6 months to 10 years) – Such children are at increased risk of Reye syndrome after influenza.^{104,105}
- *Preterm infants* (<37 weeks gestation) – These infants have an increased risk of complications from influenza (refer to 3.3.2 *Vaccination of women who are planning pregnancy, pregnant or breastfeeding, and preterm infants*).^{106,107}

Other groups

- *Residents and staff (including volunteers) of aged care and long-term residential facilities* – Annual influenza vaccination is recommended for residents and staff (including volunteers) of these facilities, including inmates of correctional facilities and residents of immigration detention centres, due to high rates of influenza transmission and complications during outbreaks in such facilities.^{29,99,108,109}
- *Homeless people* – The living conditions and prevalence of underlying medical conditions among homeless people will predispose them to complications and transmission of influenza.
- *Carers and household contacts of those in high-risk groups* – The following groups of people can potentially transmit influenza to persons at increased risk of complications from influenza infection; vaccination of these groups is therefore recommended to protect those at risk:
 - » all healthcare providers (particularly those of immunocompromised patients)
 - » household contacts (including children ≥6 months of age) of those in high-risk groups, including providers of home care to persons at risk of high influenza morbidity
 - » staff working in early childhood education and care
 - » staff (or volunteers) providing care to homeless people.

Refer to 3.3 *Groups with special vaccination requirements*, Table 3.3.7 *Recommended vaccinations for persons at increased risk of certain occupationally acquired vaccine-preventable diseases*.

- *Commercial poultry or pork industry workers* – Vaccination using the seasonal influenza vaccine composition current at the time is recommended for poultry or piggery workers and others in regular close contact with poultry or pigs during an avian or swine influenza outbreak.¹¹⁰ Although routine seasonal influenza vaccine does not protect against avian or swine influenza, there is a possibility that a person who is infected at the same time with animal and human strains of influenza virus could act as a vessel for reassortment of the two strains to form a virulent strain, with the potential for spread from human to human (i.e. initiate a pandemic as was the case with swine influenza in 2009).¹¹¹ In addition, vaccination can also prevent the transmission of influenza from humans to animals.
- *Essential services providers* – Vaccination of those who provide essential community services will minimise disruption of essential activities during influenza outbreaks. Influenza viral infections can place considerable pressure upon both public and private healthcare services. Refer to 3.3 *Groups with special vaccination requirements*, Table 3.3.7 *Recommended vaccinations for persons at increased risk of certain occupationally acquired vaccine-preventable diseases*.
- *Workers in other industries* – Due to the high attack rate of influenza in the general population, influenza vaccination in the workplace can result in benefits such as increased productivity and reduced absenteeism among workers.¹¹² Employers should consider the benefits of offering influenza vaccine in their individual workplace. Refer to 3.3 *Groups with special vaccination requirements*, Table 3.3.7 *Recommended vaccinations for persons at increased risk of certain occupationally acquired vaccine-preventable diseases*.
- *Travellers* – Influenza vaccine is particularly relevant for travellers if influenza activity is occurring at their travel destination(s). Travellers in large tourist groups (especially those including older people), those travelling on cruises, and/or those who are likely to be in confined circumstances for days to weeks are at risk of influenza, either acquired before departure or during travel to areas of the world where influenza is currently circulating. Influenza vaccination is recommended if travelling during the influenza season, especially if it is known before travel that influenza is circulating in the destination region.¹¹³ (Refer also to 3.2 *Vaccination for international travel*.)

4.7.8 Pregnancy and breastfeeding

Influenza vaccination is recommended for pregnant women (refer to 4.7.7 *Recommendations* above) and is safe to administer during any stage of pregnancy or while breastfeeding,¹¹⁴⁻¹¹⁷ despite the product information for influenza vaccines listing pregnancy as a precaution (refer to 4.7.13 *Variations from production information* below).

Refer to 3.3 *Groups with special vaccination requirements*, Table 3.3.1 *Recommendations for vaccination in pregnancy* for more information.

4.7.9 Contraindications

The only absolute contraindications to influenza vaccines are:

- anaphylaxis following a previous dose of any influenza vaccine
- anaphylaxis following any vaccine component.

Refer to 4.7.10 *Precautions* below for persons with a known egg allergy.

4.7.10 Precautions

Persons with known egg allergy

Persons with egg allergy, including anaphylaxis, can be safely vaccinated with influenza vaccines. Several published reviews, guidelines and reports have indicated that the risk of anaphylaxis associated with influenza vaccination of egg-allergic patients is very low.¹¹⁸⁻¹²³ A 2012 review of published studies, including 4172 egg-allergic patients (of whom 513 reported a history of severe allergic reaction to egg), reported no cases of anaphylaxis following administration of inactivated influenza vaccine.¹²² The largest study in the review included 830 egg-allergic patients (of whom 164 reported a history of severe allergic reaction to egg) and only 17 (2%) of these patients experienced any adverse event.¹²⁴ All adverse events were mild; they included abdominal pain, hives and respiratory symptoms such as wheezing.

Persons with a history of egg allergy (non-anaphylaxis) can receive an age-appropriate full dose of vaccine in any immunisation setting. This includes children that are sensitised (i.e. skin prick or RAST test positive) but have not yet eaten egg. Persons with a history of anaphylaxis to egg should be vaccinated in medical facilities with staff experienced in recognising and treating anaphylaxis. The vaccinated person should remain under supervision in the clinic for at least 30 minutes after vaccination. A full age-appropriate vaccine dose should be used. There is no need to split the dose into multiple injections (e.g. a test and then remainder of the dose).

Recommendations for administration of influenza vaccine in egg-allergic individuals are summarised in Table 4.7.2.

Anaphylaxis following a previous dose of any influenza vaccine is a contraindication to future influenza vaccination.

Table 4.7.2: Recommended administration of influenza vaccine in egg-allergic individuals

Allergy	Vaccine administration and setting
Sensitised but not yet eaten egg	Vaccinate with full age-appropriate dose in any immunisation setting
Non-anaphylaxis egg allergy	
Anaphylaxis egg allergy	Vaccinate with full age-appropriate dose in medical facility with staff experienced in recognising and treating anaphylaxis

Refer also to ‘Vaccination of persons with a known egg allergy’ in 3.3.1 *Vaccination of persons who have had an adverse event following immunisation*.

Persons with a history of Guillain-Barré syndrome

Persons with a history of Guillain-Barré syndrome (GBS) have an increased likelihood in general of developing GBS again, and the chance of them coincidentally developing the syndrome following influenza vaccination may be higher than in persons with no history of GBS.¹²⁵ Diagnosis of GBS is complex and must be made by a physician (refer to 3.3.3 *Vaccination of immunocompromised persons* ‘Persons with autoimmune diseases and other chronic conditions’). Individual concerns should be discussed and expert advice sought from the treating physician and/or an immunisation specialist when considering influenza vaccination for a person with a history of GBS.

Children requiring both influenza and 13-valent pneumococcal conjugate vaccine

One study has demonstrated a slightly higher risk of fever and febrile convulsions in children aged 6 months to <5 years (especially those aged 12–24 months) with the concurrent administration of inactivated trivalent influenza vaccine and 13vPCV (compared with giving the vaccines separately).¹²⁶ The risk was estimated to be about 18 excess cases per 100 000 doses in children aged 6–59 months, with a peak of 45 per 100 000 doses in those aged 16 months. Given that the reported increase in risk was relatively small, and a more recent study did not demonstrate the same association between febrile seizures and the concurrent administration of these two vaccines,¹²⁷ administration of 13vPCV and

inactivated trivalent influenza vaccine at the same visit is acceptable when both vaccines are indicated. (Refer also to 4.13 *Pneumococcal disease*.)

4.7.11 Adverse events

Fever, malaise and myalgia occur commonly, in 1 to 10% of persons who receive inactivated standard TIVs.¹²⁸⁻¹³³ These adverse events may commence within a few hours of vaccination and may last for 1 to 2 days.¹²⁸⁻¹³⁰ In children <5 years of age, these side effects may be more pronounced. In 2010, an excess of fever and febrile convulsions following influenza vaccination was reported in children aged <5 years, particularly children aged <3 years. This was associated only with one manufacturer's vaccine (Seqirus [previously bioCSL] Fluvax and Fluvax Junior); following vaccination with this vaccine, febrile convulsions occurred at a rate of 4.4 per 1000 doses in children <5 years of age.¹³⁴ This vaccine is no longer available in Australia.

Local adverse events (induration, swelling, redness and pain) occur in more than 10% of vaccine recipients, following IM administration of standard TIV.^{129,130,133} Studies directly comparing trivalent and quadrivalent inactivated influenza vaccine formulations in children and adults have demonstrated a similar safety profile.^{67,135-137}

A higher rate of injection site reactions has been observed in clinical trials with the high-dose and adjuvanted TIVs registered for use in adults aged ≥ 65 years, compared with standard TIVs. Approximately 30% of Fluzone[®] High-Dose and Flud[®] recipients reported injection site reactions, compared to approximately 20% of recipients of standard TIVs; both groups reported similar rates of systemic reactions (approximately 30%). More injection site reactions in the week after vaccination are also seen with the adjuvanted TIV when compared to non-adjuvanted TIV (approximately 35% versus 18%).⁴³ However, severe or serious adverse events have not been observed at a higher frequency in clinical trials or post-licensure surveillance studies with either the high-dose or adjuvanted vaccine.^{40,43,138-140} While high-dose and adjuvanted TIVs are only registered for use in persons aged ≥ 65 years (and are not currently recommended in younger ages), clinical trials in some younger populations and post-licensure safety data following inadvertent administration to younger people suggest a similar safety profile to that observed in persons aged ≥ 65 years.¹⁴¹⁻¹⁴³

Post-vaccination symptoms may mimic influenza infection. However, none of the influenza vaccines currently available in Australia contain live influenza viruses, so they cannot cause influenza.

Immediate adverse events (such as hives, angioedema or anaphylaxis) are very rare consequences of influenza vaccination and probably represent an allergic response to a residual component of the manufacturing process, most likely egg protein.^{118,123} However, persons with a history of anaphylaxis after eating eggs or a history of a severe allergic reaction following occupational exposure to egg protein may receive influenza vaccination after medical consultation^{118,123} (refer to 'Persons with known egg allergy' in 4.7.10 *Precautions*).

A small increased risk of GBS was associated historically with one influenza vaccine in the United States in 1976, but, since then, close surveillance has shown that GBS has occurred at a very low rate of up to 1 in 1 million doses of influenza vaccine, if at all.¹⁴⁴ Diagnosis of GBS is complex and must be made by a physician (refer to 'Uncommon/rare AEFI' in 2.3.2 *Adverse events following immunisation*).

Narcolepsy (sudden sleeping illness) has been described in association with AS03-adjuvanted pandemic influenza vaccines, predominantly in the Scandinavian population and particularly in children.¹⁴⁵⁻¹⁴⁷ These vaccines were not used and are not available in Australia. The only registered adjuvanted influenza vaccine in Australia contains a different adjuvant (squalene-based MF59 oil-in-water emulsion adjuvant). Narcolepsy has not been identified in association with influenza vaccine containing MF59 adjuvant, although the number of subjects aged <20 years in these studies was limited.^{148,149}

4.7.12 Public health management of influenza

Laboratory-confirmed cases of influenza are notifiable in all states and territories in Australia. Detailed information regarding the management of influenza cases and contacts can be found in the national guidelines for control of influenza¹⁵⁰ (www.health.gov.au/cdnasongs).

Further instructions about the public health management of influenza, including in residential care facilities, can also be obtained from state/territory public health authorities (refer to Appendix 1 *Contact details for Australian, state and territory government health authorities and communicable disease control*).

4.7.13 Variations from product information

The product information for influenza vaccines lists allergy to egg as a contraindication. The ATAGI recommends instead that patients with egg allergies can be vaccinated with an age-appropriate influenza vaccine. Refer to 4.7.10 *Precautions* above.

The product information for influenza vaccines lists pregnancy as a precaution. The ATAGI instead recommends that inactivated influenza vaccine can be given during any stage of pregnancy. Refer to 4.7.7 *Recommendations* above.

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A full reference list is available on the electronic *Handbook* or website www.immunise.health.gov.au.

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